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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,946	01/22/2001	Francois Mallet	028662.96	1475

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OLIFF & BERRIDGE, PLC  
P.O. BOX 19928  
ALEXANDRIA, VA 22320

EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 11/13/2002

*[Handwritten signature]*

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/680,946

Applicant(s)

MALLET ET AL.

Examiner

Jeffrey Fredman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 January 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Reissue Information***

1. The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.
2. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,817,465 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

3. Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

### ***Sequence Rules***

4. The current case fails to meet sequence rules because no new CRF has been submitted. However, the following paragraph, or language having the same effect, can be used to invoke the procedures of 37 C.F.R. 1.821(e) in which an identical computer

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readable form from another application is used in a given application. The paragraph should be incorporated into a separate paper to be submitted in the given application:

The computer readable form in this application, 09/680,946, is identical with that filed in application number 08/412,228, filed March 27, 1995. In accordance with 37 C.F.R. 1.821(e), please use the only computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary changes in application number and filing date for the computer readable form that will be used for the instant application.

A paper copy of the Sequence Listing should be attached to the form for entry into the originally filed specification of the instant application.

### ***Double Patenting***

5. Claims 1-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,654,143. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-18 of U.S. Patent 5,654,143 anticipate the current claims.

Claims 1-18 of U.S. Patent 5,654,143 teach a method for the amplification of RNA in a sample, comprising:

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a) obtaining a starting solution by adding to a container the sample, a buffer, a first primer, a second primer, a plurality of nucleotide triphosphates, a sufficient amount of an enzyme system having reverse transcriptase activity and a heat stable enzyme system having DNA polymerase activity, and closing the container, wherein said sufficient amount is an amount which, after the heat treatment of step b) below, will retain sufficient reverse transcriptase activity to permit performance of step c) hereafter;

b) heating the solution obtained in a) to a temperature of 60.degree.-75.degree. C. and maintaining said temperature for a sufficient time to provide denaturation of said RNA without inactivating the enzyme system having reverse transcriptase activity, said time ranging from 1 minute to 15 minutes;

c) bringing the solution obtained in b) to a predetermined temperature of at least 50.degree. C. and maintaining said temperature for sufficient time whereby a first cDNA strand is synthesized and a RNA-cDNA heteroduplex is formed;

d) heating the solution obtained in c) to a predetermined temperature whereby said RNA-cDNA heteroduplex is denatured to form an RNA single strand and a first cDNA single strand;

e) cooling the solution obtained in d) to a predetermined temperature and maintaining said temperature for a sufficient time whereby the second primer hybridizes with the first cDNA strand;

f) bringing the solution obtained in e) to a predetermined temperature and maintaining said temperature for a sufficient time whereby a second cDNA strand is synthesized to form a double-stranded cDNA; and

g) denaturing the double-stranded cDNA and subjecting the cDNA strands to a sufficient number of amplification cycles to obtain a desired amount of amplified product.

The claims further teach wherein in step b) said solution is heated to at least 65.degree. C or wherein in step c) said predetermined temperature is a temperature which permits the hybridization of the first primer to said RNA without permitting hybridization of the primer to an RNA sequence that is not absolutely complementary.

The claims further teach wherein in step c) said predetermined temperature is between 50.degree. and 65.degree. C and where in step c) said sufficient time is less than about 15 minutes.

The claims further teach an enzyme system having reverse transcriptase activity selected from the group consisting of avian myoblastosis virus and Moloney murine leukemia virus wherein the amounts of reverse transcriptase activity and of DNA polymerase activity are such that the ratio of units of reverse transcriptase to units of DNA polymerase is from 2 to 8.

The claims further teach SEQ ID NO:s 1 and 2.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

### ***Reissue Rejections***

Claims 1-34 are rejected under 35 U.S.C. 251 as being broadened in a reissue application filed outside the two year statutory period. Specifically, the error identified in the oath is that the claim is confusing and may be limited to adding components to the sample after the sample is added to the container based upon the language "obtaining a starting solution by adding to a container comprising the sample, a buffer, a first primer . . . ." The correction which is desired is that the claim should literally cover addition of the ingredients in any order. This same asserted error was present in U.S. patent 5,654,143 where the claim also used the language "obtaining a starting solution by adding to a container comprising the sample, a buffer, a first primer . . . ." Therefore, the error that was present is in an application which issued more than two years prior to the filing of this reissue. These claims are being broadened in an application filed more than two years after the issue of U.S. Patent 5,654,143. A claim is broader in scope

than the original claims if it contains within its scope any conceivable product or process which would have infringed the original patent. A claim is broadened if it is broader in any one respect even though it may be narrower in other respects.

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 3, 4, 8-12, 14, 19, 22-25 and 27-34 are rejected under 35

U.S.C. 102(b) as being anticipated by Sellner et al (Nucleic Acids Research (April 11, 1992) 20(7):1487-1490).

Sellner teaches a method for the amplification of RNA, in a sample (abstract), comprising:

a) obtaining a starting solution by adding to a container comprising the sample, a buffer, a first primer, a second primer, a plurality of nucleotide triphosphates, a sufficient amount of an enzyme system having reverse transcriptase activity, here the AMV reverse transcriptase and a heat stable enzyme system having DNA polymerase activity, here Taq DNA polymerase (see page 1488, subheading "RT-PCR"),

closing the container, wherein said sufficient amount is an amount which, after the heat treatment of step b) below, will retain sufficient reverse transcriptase activity to permit performance of step c) hereafter (see 1488, subheading "RT-PCR",) here overlay with mineral oil and then put in PCR machine,

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b) heating the solution obtained in a) to a temperature sufficient to permit denaturation, here a heating for 60 minutes at 42 C to denature RNA while maintaining AMV reverse transcriptase activity which temperature permits specific hybridization (page 1488, subheading "RT-PCR"),

c) bringing the solution obtained in b) to a predetermined temperature and maintaining said temperature for sufficient time whereby a first cDNA strand is synthesized and a RNA-cDNA heteroduplex is formed (page 1488, subheading "RT-PCR"),

d) heating the solution obtained in c) to a predetermined temperature whereby said RNA-cDNA heteroduplex is denatured to form an RNA single strand and a first cDNA single strand ((page 1488, subheading "RT-PCR"), here the PCR amplification at 94 C denaturation step),

e) bringing the solution obtained in d) to a predetermined temperature and maintaining said temperature for a sufficient time whereby the second primer hybridizes with the first cDNA strand; (see page 1488, subheading "RT-PCR") here the PCR amplification at 60 C annealing step,

f) bringing the solution obtained in e) to a predetermined temperature and maintaining said temperature for a sufficient time whereby a second cDNA strand is synthesized to form a double-stranded cDNA; and (see page 1488, subheading "RT-PCR") here the PCR amplification at 72 C extension step,

g) denaturing the double-stranded cDNA and subjecting the cDNA strands to a



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sufficient number of amplification cycles to obtain a desired amount of amplified product (see page 1488, subheading "RT-PCR" which teaches the use of 35 cycles.

Sellner teaches performance of the method with a ratio of RT to DNA polymerase of from 2 to 4 (see page 1488, column 2, subheading "ratio of Taq polymerase to RT).

3. Claims 1-4, 7, 11, 12, 14, 18-23 and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Myers et al (Biochemistry (1991) 30(31):7661-7666)..

As an initial matter, the claim was interpreted for purposes of the following rejection as being open and permitting additional steps due to the use of the transitional term "comprising". As MPEP 2111.03 notes "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps." Thus, while after step a), the container is closed, this claim does not preclude or prevent an additional unrecited step of opening the container and adding additional reagents. Further, there is no requirement that the first and second primer be different. Thus, addition of a solution which contains a plurality of molecules of a single primer meets this claim requirement. Similarly in claim 23, there is no requirement that the first and second enzyme be different. Thus, the Tth polymerase, which has both activities, meets the requirement of this claim.

Myers teaches a method for the amplification of RNA, in a sample (abstract), comprising:

a) obtaining a starting solution by adding to a container comprising the sample, a buffer, a first primer, a second primer, a plurality of nucleotide triphosphates, a

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sufficient amount of an enzyme system having reverse transcriptase activity and a heat stable enzyme system having DNA polymerase activity (see page 7662, column 2, subheading "RT/PCR coupled reactions"), where the Tth polymerase inherently has both reverse transcriptase and DNA polymerase activities (see figures 1 and 3),

closing the container, wherein said sufficient amount is an amount which, after the heat treatment of step b) below, will retain sufficient reverse transcriptase activity to permit performance of step c) hereafter (see page 7662, column 2, overlay with mineral oil);

b) heating the solution obtained in a) to a temperature sufficient to permit denaturation, here a heating at 15 minutes at 70 C to denature RNA while maintaining Tth polymerase activity which temperature permits only specific hybridization (page 7662, column 2),

c) bringing the solution obtained in b) to a predetermined temperature and maintaining said temperature for sufficient time whereby a first cDNA strand is synthesized and a RNA-cDNA heteroduplex is formed (page 7662, column 2);

d) heating the solution obtained in c) to a predetermined temperature whereby said RNA-cDNA heteroduplex is denatured to form an RNA single strand and a first cDNA single strand (see page 7662, column 2, PCR amplification at 95 C denaturation step),

e) bringing the solution obtained in d) to a predetermined temperature and maintaining said temperature for a sufficient time whereby the second primer

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hybridizes with the first cDNA strand; (see page 7662, column 2, PCR amplification at 60 C annealing and extension step),

f) bringing the solution obtained in e) to a predetermined temperature and maintaining said temperature for a sufficient time whereby a second cDNA strand is synthesized to form a double-stranded cDNA; and (see page 7662, column 2, PCR amplification at 60 C annealing and extension step)

g) denaturing the double-stranded cDNA and subjecting the cDNA strands to a sufficient number of amplification cycles to obtain a desired amount of amplified product (see page 7662, column 2, where Myers teaches use of the 35 cycles).

Myers teaches that RT can be performed at 42 C, which is between 40 and 50 C (see page 7662, column 2).

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2, 5-7, 13, 18, 20, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sellner et al (Nucleic Acids Research (April 11, 1992) 20(7):1487-1490) as applied to claims 1, 3, 4, 8-12, 14, 19, 22-25 and 27-34 in view of Shimomaye et al (Gene. Anal. Techn. (1989) 6:25-28).

Sellner teaches a method for the amplification of RNA, in a sample (abstract), comprising:

a) obtaining a starting solution by adding to a container comprising the sample, a buffer, a first primer, a second primer, a plurality of nucleotide triphosphates, a sufficient amount of an enzyme system having reverse transcriptase activity, here the AMV reverse transcriptase and a heat stable enzyme system having DNA polymerase activity, here Taq DNA polymerase (see page 1488, subheading "RT-PCR"),

closing the container, wherein said sufficient amount is an amount which, after the heat treatment of step b) below, will retain sufficient reverse transcriptase activity to permit performance of step c) hereafter (see 1488, subheading "RT-PCR",) here overlay with mineral oil and then put in PCR machine,

b) heating the solution obtained in a) to a temperature sufficient to permit denaturation, here a heating for 60 minutes at 42 C to denature RNA while maintaining AMV reverse transcriptase activity which temperature permits specific hybridization (page 1488, subheading "RT-PCR"),

c) bringing the solution obtained in b) to a predetermined temperature and

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maintaining said temperature for sufficient time whereby a first cDNA strand is synthesized and a RNA-cDNA heteroduplex is formed (page 1488, subheading "RT-PCR"),

d) heating the solution obtained in c) to a predetermined temperature whereby said RNA-cDNA heteroduplex is denatured to form an RNA single strand and a first cDNA single strand ((page 1488, subheading "RT-PCR"), here the PCR amplification at 94 C denaturation step),

e) bringing the solution obtained in d) to a predetermined temperature and maintaining said temperature for a sufficient time whereby the second primer hybridizes with the first cDNA strand; (see page 1488, subheading "RT-PCR") here the PCR amplification at 60 C annealing step,

f) bringing the solution obtained in e) to a predetermined temperature and maintaining said temperature for a sufficient time whereby a second cDNA strand is synthesized to form a double-stranded cDNA; and (see page 1488, subheading "RT-PCR") here the PCR amplification at 72 C extension step,

g) denaturing the double-stranded cDNA and subjecting the cDNA strands to a sufficient number of amplification cycles to obtain a desired amount of amplified product (see page 1488, subheading "RT-PCR" which teaches the use of 35 cycles.

Sellner teaches performance of the method with a ratio of RT to DNA polymerase of from 2 to 4 (see page 1488, column 2, subheading "ratio of Taq polymerase to RT).

Sellner does not teach heating the solution to a temperature above 42 C in order to denature the RNA to improve reverse transcription by the AMV reverse

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transcriptase. Sellner also does not teach the particular times, such as less than 15 minutes, claimed.

Shimomaye teaches that the simplest method to improve reverse transcription by the AMV reverse transcriptase is to increase the reaction temperature (see abstract and page 27, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the RT-PCR method of Sellner, which relies upon AMV reverse transcriptase, with the use of elevated temperatures for denaturation and reverse transcription by the AMV reverse transcriptase as taught by Shimomaye since Shimomaye notes "We have found that raising the temperature above 47 C is the simplest way to overcome template secondary structure (abstract)". Shimomaye further notes "We were able to read a crisp sequence from reactions run at 47 C, 50 C (figure 1) and even 55 C (see page 27, column 2)". An ordinary practitioner would have been motivated to modify the invention of Sellner, which begins with reverse transcription of RNA by AMV reverse transcriptase with the finding of Shimomaye that this transcription can be improved in a simple way by increasing the temperature up to temperatures including 55 C in order to maximize the ability of the assay to detect sequences which have template secondary structure and would otherwise be resistant to the method of Sellner. That is, an ordinary practitioner, apprised by well known prior art and by Shimomaye of RNA sequences with secondary structure which impedes reverse transcription, would have been motivated to use the increased temperatures of Shimomaye to solve this problem in a simple fashion in the Sellner method, so Sellner's

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method could be applied, as modified by the suggestion and teachings of Shimomaye, to function on RNA templates with secondary structure.

With regard to the specific time frames and temperatures for denaturation and for transcription, in the absence of a secondary consideration, these elements represent simple routine optimization. Shimomaye teaches that such conditions are optimizable for AMV RT, stating "Buffer and temperature conditions had already been optimized for the use of AMV RT in the production of cDNA (page 27, column 2)". Thus, an ordinary practitioner would have recognized that the results optimizable variables of time, and temperature could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times or temperatures for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman  
Primary Examiner  
Art Unit 1637

October 30, 2002



John J. Doll, Director  
Technology Center 1600